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DOI:

[10.1126/scitranslmed.aab0194](https://doi.org/10.1126/scitranslmed.aab0194)

Document Version

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Citation for published version (APA):

Manolio, T. A., Abramowicz, M., Al-Mulla, F., Anderson, W., Balling, R., Berger, A. C., Bleyl, S., Chakravarti, A., Chantratita, W., Chisholm, R. L., Dissanayake, V. H. W., Dunn, M., Dzau, V. J., Han, B. G., Hubbard, T., Kolbe, A., Korf, B., Kubo, M., Lasko, P., ... Ginsburg, G. S. (2015). Global implementation of genomic medicine: We are not alone. *Science Translational Medicine*, 7(290), [290ps13]. <https://doi.org/10.1126/scitranslmed.aab0194>

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Global Implementation of Genomic Medicine: We Are Not Alone

Running title: Global Implementation of Genomic Medicine

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This paper summarizes the deliberations of a symposium convened by the National Human Genome Research Institute on January 8-9, 2014, to examine global models for genomic medicine implementation and opportunities for collaboration. The views expressed in this article are those of the individual authors and do not necessarily represent the views of their affiliated organizations, institutions, or government agencies.

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Word count: Abstract: 243
 Text: 3,990

Conflict of Interest Notification:

ABSTRACT

Advances in high-throughput genomic technologies coupled with a growing number of genomic results potentially useful in clinical care have led to ground-breaking genomic medicine implementation programs in various nations. Many of these innovative programs capitalize on unique local capabilities arising from the structure of their health care systems or their cultural or political milieu, as well as from unusual burdens of disease or risk alleles. Many such programs are being conducted in relative isolation and might benefit from sharing of approaches and lessons learned in other nations. The National Human Genome Research Institute recently brought together 25 of these groups from around the world to describe and compare projects, examine the current state of implementation and desired near-term capabilities, and identify opportunities for collaboration to promote the responsible implementation of genomic medicine.

The wide variety of nascent programs in diverse settings demonstrates that implementation of genomic medicine is expanding globally in varied and highly innovative ways. Opportunities for collaboration abound in the areas of evidence generation, health information technology, education, workforce development, pharmacogenomics, and policy and regulatory issues. Several international organizations that are already facilitating effective research collaborations should engage to ensure implementation proceeds collaboratively without potentially wasteful duplication. Efforts to coalesce these groups around concrete but compelling signature projects, such as global eradication of genetically-mediated drug reactions or developing a truly global genomic variant data resource across a wide number of ethnicities, would accelerate appropriate implementation of genomics to improve clinical care world-wide.

Key words: medical genomics, implementation, global collaborations, practice standards, pharmacogenomics, personalized medicine, precision medicine

INTRODUCTION

The growing number of genomic advances directly relevant to disease diagnosis, treatment, and prevention [1] coupled with the declining cost of detection of genomic variation [2] has opened the door to using genomic technologies in routine clinical care. Among the many challenges to widespread implementation of genomic medicine, the lack of evidence of impact on clinical outcomes is key and looms large in terms of the effort needed to address it [3]. Other barriers include needs for standardization and quality assurance of genomic data produced by clinical laboratories, clinical informatics infrastructure for managing genomic information, education for health professionals and patients in using the information, and policies for data sharing that permit ongoing capture of generalizable clinical experience in what has been termed “evidence-generating medicine” [4].

A host of ongoing efforts worldwide to establish national implementation strategies for genomic medicine reflects the growing level of discovery and understanding in this area [5-8], but many such efforts are being conducted in relative isolation. Sharing strategies, data, and standards could minimize wasteful duplication and speed progress in identifying genomics-based interventions most likely to improve patient care and enhance outcomes for patients and populations. Early efforts at such collaborations include the European Association for Predictive, Preventive, and Personalised Medicine (EPMA) [9], the European Commission’s EuroBioForum and Observatory [10] and the Genomic Medicine Alliance [11,12], which have spearheaded promising projects such as the application of genome sequencing in pharmacogenomics and development of online pharmacogenomic resources. Related efforts include the International Rare Disease Research Consortium (IRDiRC), developing new diagnostic strategies and therapies for rare diseases [13]; the Global Alliance for Genomics and Health (GA4GH), promoting responsible sharing of genomic data for research [14]; and EuroGentest, drafting professional guidelines for diagnostic DNA sequencing [15].

To assess the current global state-of-the-art, and building on early genomic medicine implementation efforts in the U.S. [3], the National Human Genome Research Institute [16] and the Institute of Medicine of the U.S. National Academy of Sciences convened 90 leaders in genomic medicine from the U.S. and 25 other countries on 5 continents for a “Global Leaders in Genomic Medicine” symposium in January 2014 [17]. While the organizers attempted to identify and invite every nation working in genomic medicine implementation, participation was undoubtedly limited by the lack of systematic information on such efforts and limited funding for participation. Despite these constraints, several countries outside of Europe, the U.K. and the U.S. were able to take part, such as Australia, Estonia, India, Israel, Japan, Korea, Kuwait, New Zealand, Singapore, Sri Lanka, and Thailand [see full list of participating countries at <http://www.genome.gov/27555775>]. This paper summarizes the efforts described by these groups, with emphasis on regions with unique capabilities due to the structure of their health care systems, cultural or political readiness for implementation, or unusual disease burdens or risk-allele frequencies; the current state of implementation in these countries and desired capabilities in the next 3-5 years; and opportunities for collaboration to promote the responsible implementation of genomic medicine.

BRIEF LANDSCAPE OF INTERNATIONAL GENOMIC MEDICINE PROJECTS

In an informal poll of participants prior to the symposium, nearly all sites reported some genomic medicine capabilities such as using genotyping and/or genome or exome sequencing for disease prediction, diagnosis, prevention, and treatment as well as family counseling (Table 1). Over 70% of respondents reported availability of clinical sequencing resources for cancer treatment, rare disease diagnosis, and microbial pathogen identification in specialized centers only, while another ~10% reported these capabilities to be widely available. Conversely, more than half reported lack of any capabilities for newborn sequencing, RNA profiling, metabolomics or proteomics. Substantial gains in availability of clinical genomic resources

were desired in the next 3-5 years, particularly for pharmacogenomics, pathogen identification, genetic counseling, electronic medical records, and clinical decision support. Several other technologies, such as newborn sequencing, rare disease diagnosis, and RNA profiling, were projected to become available in specialized centers where no capability currently exists. Barriers to global implementation of genomic medicine (Table 2) were similar to those identified in a 2012 survey examining U.S. genomic medicine implementation efforts [3], reinforcing the notion that the global genomic medicine community shares important challenges and interests.

The most common implementation efforts involve cancer genomics, large-scale exome or whole-genome sequencing, and pharmacogenomics, while several current projects focus on particular national priorities (Table 3). National efforts to build infrastructure for genome sequencing and other genomic and information technologies are underway in nearly all countries represented. Perhaps the largest such effort is the UK project to sequence 100,000 whole genomes by 2017 through the creation of Genomics England [18]. This project builds on a national strategy to link National Health Service (NHS) electronic medical records (EMRs) to research and development of genomic medicine [5,19], focusing initially on NHS patients with cancer and rare and infectious diseases. The sequenced genomes will be analyzed to enhance each patient's clinical care as well as create a research dataset of genomic data linked to EMRs. Genomics England also aims to train the wider health care community in using the technology and will build secure data linkages to the NHS to ensure the effort leads to better patient care. Pilot studies of 2,000 patients with rare inherited diseases will be completed by early 2015, and pilot studies of 3,000 patients with lung, breast, and colon cancer began in late 2014. The main study will involve sequencing of 30,000 whole genomes per year in these three emphasis areas through 2017 and should produce a rich infrastructure of next-generation genome sequencing centers, a sample pipeline and biorepository, and large-scale data resources for producing new diagnostics and therapies.

Belgium is also building a national genome-sequencing pipeline, the Belgian Medical Genomics Initiative (BeMGI [20])-- a comprehensive network of scientists and clinicians intended to boost research, translate genomics into clinical care, and prepare the next generation of researchers and clinicians to use genomic technologies. Important current efforts are devoted to collecting and sharing variant frequency data and translating next generation genome sequencing into clinical practice. Similarly, the Estonian government recently approved the Pilot Program for Personal Medicine, involving the sequencing of 5,000 Estonians and development of an Estonian-specific genotyping array, coupled with automated decision support and training of physicians to use the results in everyday practice. This comprehensive approach will be pilot tested in 50,000 individuals within the Estonian Biobank [21] and linked with Estonia's rich national EMR system, through which all residents of Estonia can access their personal medical information via a smartcard-based National Identity Card. If successful, the resulting array-based test will then be offered to all Estonian residents ages 35-65 years, yielding a database of up to 500,000 individuals with longitudinal EMR, genotype, and prescription data for use in clinical disease risk assessment and drug response prediction as well as in research.

Israel's Clalit health system has established a national laboratory that provides all medical institutes in Israel with sequencing-based panels assessing tissue and germline genomic changes for risk and treatment response. It is also testing extensively for founder mutations in different disease states and is developing models of primary care in which patients will be routinely tested with broad genomic panels and by staff trained to interpret genomic results. In Australia, newly developing comprehensive cancer centers are integrating genomics-based cancer research, patient care, and education while giving patients access to the latest experimental protocols and drugs. Several other countries such as Korea and Kuwait are pursuing more limited genome sequencing programs, some in close collaboration with the private sector, to build capacity and expertise. These and many other participating nations

expressed willingness to deposit their resulting sequence and phenotype data in widely accessible databases such as ClinVar [22] or dbGaP [23]. Such sharing will not only facilitate interpretation of human genomic variation globally but will also give external visibility to these nations' emerging programs and better integrate their scientists into the international genomics research community.

Canada's Genomics and Personalized Health Competition (GAPH) is a somewhat different approach to building national genomics capacity and assessing the cost-effectiveness and impact of genomic technologies on patient outcomes [8]. Seventeen projects have been funded to support genomic medicine implementation and related research in health administration, health technology, and comparative effectiveness. Close involvement of the private sector is an important and innovative component and is reflected in the participation of 19 biotechnology-oriented companies in the project teams. Private sector involvement is also critical to Kuwait's Genatak sequencing initiative in which patients pay for their whole genome sequencing themselves [24]. Japan is implementing a program somewhat similar to Canada's GAPH in its "Implementation of Genomic Medicine Project" to establish a network of genomics-focused biobanks, build a comprehensive genomic variation database, and perform studies to assess clinical efficacy and utility of genomic information in clinical practice.

A third approach-- utilizing highly focused pilot programs to build capacity and demonstrate effectiveness before full-scale implementation-- capitalizes on disproportionate disease burdens or unique capabilities within a given country. Luxembourg's Centre for Systems Biomedicine, for example, is leveraging local expertise in neurobiology, pathway analysis, and community-driven annotation [25,26] to create an interactive map charting genetic and molecular underpinnings of Parkinson disease [27]. This will be integrated with genome sequence data to facilitate early diagnosis and molecular stratification of the disease. Singapore's Personalized OMIC Lattice for Advanced Research and Improving Stratification (POLARIS) project takes advantage of local expertise and interest in genomics and

ophthalmology in launching a pilot effort of *TGFBI* sequencing to assess genetic risk for stromal corneal dystrophies [28]. This will be followed by implementation of a 90-gene panel targeting gastrointestinal cancers, diseases of high burden in Singapore, in a systematic effort to develop a nationwide framework for genetic and genomic testing.

Thailand's Ministry of Public Health and Ramathibodi Hospital are focusing on a condition occurring at unusually high frequency in that region and recently shown to have strong genetic determinants. Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is a devastating and often fatal cutaneous reaction to medications that is largely mediated by high-risk HLA alleles. Thailand has one of the highest rates of SJS/TEN in the world, mainly attributable to high frequency of these risk alleles and use of causative drugs [28]. Ramathibodi Hospital has launched a "pharmacogenetics card" that provides patients' HLA variant information predicting risk of SJS/TEN from specific drugs on a patient-carried wallet card. Initial cost-effectiveness studies have been sufficiently convincing that the Thai government has agreed to provide the testing as standard of care [29-31]. Singapore has come to the same conclusion and Asian patients being considered for carbamazepine are offered *HLA-B*15:02* screening [32,33].

These three briefly described approaches—population-wide genomic sequencing and EMR integration, coordinated nationwide genomic medicine research programs, and localized efforts focusing on unique capabilities or needs—demonstrate that no country has a monopoly on implementation of genomic medicine. Quite the contrary, implementation is expanding globally in diverse and highly innovative ways. Yet here again, as noted in early U.S. genomic medicine implementation programs [3], many of these efforts are being conducted in relative isolation with little interaction or collaboration. Given the rapid growth of the genomics-based biotechnology sector [34] and the pressure on university-based researchers to commercialize their work [35], some degree of competition is to be expected. Still, willingness to share effective tools and strategies through consortia such as the Electronic Medical Records and

Genomics (eMERGE) Network [36], the Pharmacogenomics KnowledgeBase (PharmGKB [37]), the Implementing Genomics in Practice (IGNITE) Network [38], and the GAPH, IRDiRC, and GA4GH efforts described above demonstrate the possibilities for synergistic global interactions. Indeed, the international collaborations identified above [11-14] predominantly focusing on research illustrate the potential power of such alliances and the readiness of the genomics community to form them. Given the critical need for clinical evidence generation and evaluation of genomic medicine interventions, and the value of harnessing information from diverse populations to capture the immensity of human genomic variation, international collaborative projects in clinical implementation are an obvious solution.

OPPORTUNITIES FOR INTERNATIONAL COLLABORATION

Areas that could benefit from multinational collaborations in genomic medicine implementation include evidence generation, health information technology, education, workforce development, pharmacogenomics, and policy and regulatory issues including economic evaluation (Table 4). Recognizing the important differences among countries in culture, public perceptions, governance structures, health care systems, resources, and infrastructure-- and notwithstanding some clear biologic differences in allele frequencies and prevalent diseases-- there is so much to be learned and the potential for unnecessary duplication is so great that some degree of coordination and sharing of results is critical.

Evidence Generation

Generating evidence of the value of genomics for patients, clinicians, and health care systems is among the most expensive of potential international collaborations and already has considerable work ongoing, as detailed above. Despite differences in health care delivery systems, much can be learned from clinical trials and demonstration projects in other settings, as is clear from other disciplines [39-41]. International collaborations have amply shown the

speed with which multi-national consortia can answer questions that few countries can tackle on their own, as demonstrated for survival after myocardial infarction [42], global burden of disease [43], and HIV/AIDS [44]. Given the many genomic medicine implementation projects already in progress, a critical first step is to catalog ongoing evidence-generating projects and the genomics-based interventions they can be used to evaluate. Such a catalog should include the availability of these projects' specimens and data, including patient data, for additional research. Registries such as the Australian New Zealand Clinical Trials Registry [45], the European Union Clinical Trials Register [46], and ClinicalTrials.gov [47,48], could conceivably be adapted to receive and provide information about genomic medicine evidence generation projects.

To fill gaps in evidence identified by surveying the catalogued projects, a key next step is to identify countries and health care systems willing to enable access to patient data, within appropriate constraints of policy, privacy, and consent. Differences across systems, including but not limited to language, will also need to be evaluated to find those most scientifically advantageous for combined analysis. Systems will then be needed to capture relevant outcomes from EMRs and other clinical systems and settings, and to analyze and interpret the findings. Funding for these efforts will of course be needed, but to the degree that studies can be embedded in ongoing clinical care, costs of evidence generation may be significantly reduced [49-51].

Another important step is to define standards for what constitutes sufficient evidence to implement a genomic medicine intervention, which will likely vary depending on whether a gene, genetic variant, or genetic test is under consideration and whether it would be used for risk prediction, diagnosis, treatment, or understanding of pathogenesis. Additional standards for performance of genetic tests, with more emphasis on interpretation and clinical decision support, will also be needed, as will standards for incorporating genomic information into the EMR. Once a sufficient body of evidence is available, professional practice guidelines suitable

to a specific setting or country will need to be developed. Along these lines, Australia and New Zealand's National Health and Medical Research Councils are developing a framework and principles to facilitate the translation of genomic-based tests from discovery to health care [52].

Health Information Technology

Few areas of medicine, with the possible exception of imaging, are as dependent on information technology (IT) as genomics, given the vastness of genome sequence data. Although sequence data can and likely should be stored and manipulated outside the EMR [53], extracting even the clinically relevant genomic variants found in a single patient is a challenging task. Due to the rapid evolution of knowledge about clinically relevant variants and the changing clinical situation of an individual patient, a dynamic approach is needed for presenting variant information only when it can potentially make a difference in that individual's care [54]. In addition, genome sequence data should ideally be retrievable for use later in a patient's clinical course, and throughout their lifetime, and should be accessible to other specialists and care systems as needed.

A critical first step is to define the key data elements that should be stored in the EMR, so that construction of IT systems can accommodate them. Truly global resources for actionable clinical genomic variants are urgently needed and could build on current efforts such as the Clinical Genome Resource (ClinGen) [55,56] that includes the ClinVar database of the National Center for Biotechnology Information [22]. Other federated databases necessary to interpret variants and implement genomic medicine, such as the international Exome Aggregation Consortium (ExAC) Data Set [57] and the Sanger Institute's Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER) [58] will also be needed, as will collection and aggregation of worldwide genomic variant data and agreed-upon strategies to create relevant reference genome sequences where needed to underpin these resources. Use of available and widely accepted controlled vocabularies (ontologies) for

phenotypes and avoidance of proliferation of local or regional ontologies will be essential to interpretation of variants and sharing of information. The Innovative Medicine Initiative (IMI) project "ETRIKS," funded jointly by the European Union and industry, aims to create and run an open, sustainable research informatics and analytics platform for sharing data and supporting translational research in personalized medicine [59].

Education and Workforce Development

Educational needs will vary by the group to be targeted, be they health practitioners or the lay public (Table 4). Assessments of the currently available genomic professional workforce and estimates of workforce needs, while likely to show shortages at almost every level in almost every country, will help to prioritize educational programs. Programs should also be tailored to the settings in which genomics-based care is expected to be delivered, such as through routine primary care, specialized genetic clinics, or pharmacists or other allied health personnel. Competencies for health care professionals at multiple levels within a given system will need to be defined and appropriate educational programs developed [60,61]. Integration of genomics into health professional curricula will become increasingly necessary [62]. As materials developed in one part of the world are shared globally, translation for language and cultural appropriateness will be needed, but will be worthwhile if effective training paradigms and best practices can be identified and shared rather than invented (or re-invented) *de novo*. Relying increasingly on distance learning and other online tools [63,64] will facilitate rapid implementation and global spread.

Education and engagement of the public, including policy-makers and regulators, should also build on available resources that can be translated and adapted to specific cultures [65,66]. A “clearinghouse” for accumulated information and introduction of novel educational materials would be useful. As elsewhere, customizing materials to the culture of the target audience will be critical for facilitating understanding and acceptance.

Pharmacogenomics

Several pharmacogenomic applications have already been widely implemented in the U.S. and elsewhere [1,67,68] and could represent an “early win” ripe for trans-national sharing of best practices and lessons learned. Effective international collaborations have been formed to study the genomics of adverse drug reactions [69-71], but actual implementation efforts have been more isolated. The Pharmacogenetics for Every Nation Initiative (PGENI) is a notable exception, promoting integration of pharmacogenomics into public health decision-making by using population-specific risk allele frequency data for nationally-tailored drug selection in developing nations [72]. Guidelines from the Pharmacogenomics Research Network’s Clinical Pharmacogenetics Implementation Consortium (CPIC [73]), which provides recommendations on drug selection and dosing based on an individual’s genotypic data, are also increasingly used clinically.

Collaborative implementation efforts in pharmacogenomics could promote generation of an improved evidence base, focusing particularly on inexpensive drugs characterized by treatment failure such as clopidogrel [74], or severe adverse reactions such as abacavir [75], and likely to be limited to a genetically defined subset. The pharmacogenomics card for avoidance of SJS/TEN being implemented in Thailand, as described above, is an elegantly simple and practical approach for reducing the incidence of one of the most feared of all adverse drug reactions. Wider implementation of this approach in neighboring countries with similar health systems and ancestries, with an ultimate aim of global eradication of genetically-related SJS/TEN, appears to be an achievable goal around which an international genomic medicine collaborative could coalesce.

Application of whole-genome sequencing in pharmacogenomics could eventually define fully an individual’s personalized pharmacogenomics profile [76]. Customizing such an approach as a targeted sequencing effort of the several hundred pharmacogenes involved in

drug metabolism and transport, or the smaller subset of clinically actionable pharmacogenes [37] would reduce costs and make this application more affordable than more comprehensive sequencing efforts [77].

Policy and Regulatory Issues

Multiple international initiatives are addressing policy needs to facilitate data sharing in genomic research, particularly the Canadian-led Public Population Project in Genomics (P3G) [78] and GA4GH [14,79]. Such efforts are quite relevant to genomic medicine implementation and, as with the evidence realm, an assessment of current activities along with a gap analysis would be important initial steps. Harmonizing national ethical guidelines and regulatory frameworks as feasible will be essential for successful international collaborations, as will a more complete understanding of regional laws relevant to genomics governing research, privacy, and confidentiality. In evaluating costs, risks, and benefits of genomic interventions, identifying conditions for which genomic tools could have the greatest impact on patient and population outcomes-- such as cancer, metabolic disorders, HIV therapy, or cystic fibrosis-- would be a useful first step. By integrating economic assessments into translational research not only can the utility of genomic interventions be determined, but the relative value of such interventions can be assessed and inform health care decision-makers. Expanding single-country studies of cost-effectiveness to multiple health care systems may help identify key underpinning structural components that promote favorable cost-benefit ratios [80]. Multi-national collaborations will be particularly valuable for examining different systems and models,

such as those with one or a few centralized payers that can provide a more unified and systematic examination of the decision-making process.

Useful next steps include conducting a more systematic mapping effort of ongoing implementation projects worldwide and an inventory of available evidence and evidence-generation projects. These will help to define gaps that a group devoted primarily to implementation can fill and how best that group can interact with existing efforts.

CONCLUSION

The wealth of international programs actively engaged in genomic medicine implementation, and the potential for synergy and collaboration among them, present exciting opportunities for speeding progress and improving care. Especially in this online age, none of these projects should have to labor in isolation. Several organizations are already showing the power of the international genomics community to form effective collaborations around research [10-14], though most are closer to the generation of new knowledge through research than to implementation of that knowledge for improving patient care. Engaging and building upon the ongoing work of these groups will be critical in furthering the effort without wasteful duplication. Coalescing these groups around concrete but compelling signature projects may have a galvanizing effect that will facilitate similar programs in the future.

To explore these possibilities, several participating investigators and countries have formed a Global Genomic Medicine Collaborative (G2MC) hosted by the U.S. Institute of Medicine as part of its Genomic Medicine Roundtable [81]. Goals of the G2MC are to serve as a nexus for genomic medicine activities globally, develop opportunities for global genomic medicine implementation and outcomes research, and capture and disseminate best practices for genomic medicine implementation across the global community.

Recognizing that this initial survey has likely failed to capture many relevant projects and interested countries, the authors invite others, particularly scientists and policy-makers representing their governments' genomic medicine implementation efforts, to join this effort and make their interests known to the authors (particularly G.G., G.P., and J.W.). Relevant projects are characterized mainly by an individual's genomic results being used in their clinical care, and by the commitment of participating organizations to serving the needs of a global community of patients, researchers, and clinicians. Genomic medicine has the potential to dramatically change the way we train medical professionals and deliver health care. As we work toward realizing our common interests in the appropriate implementation of genomic medicine, it is indeed encouraging to know that none of us need tackle these challenges alone.

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Table 1. Selected current and desired genomic medicine capabilities across participating countries/regions (number surveyed =25).

| Capability | Today (%) | | | Desired in 3-5 Years (%) | | |
|-----------------------------------|------------|---------------------|------------------|--------------------------|---------------------|------------------|
| | Not at all | Specialized Centers | Widely Available | Not at all | Specialized Centers | Widely Available |
| Pharmacogenomics | 23 | 66 | 11 | 17 | 29 | 56 |
| Germline Sequencing | 23 | 66 | 11 | 11 | 72 | 17 |
| Tumor Sequencing | 17 | 72 | 11 | 11 | 60 | 29 |
| Newborn Sequencing | 64 | 36 | 0 | 11 | 72 | 17 |
| Maternal-Fetal Sequencing | 29 | 65 | 6 | 11 | 66 | 23 |
| Rare Disease Diagnosis | 23 | 71 | 6 | 6 | 77 | 17 |
| Microbial Pathogen Identification | 17 | 72 | 11 | 11 | 36 | 53 |
| RNA Profiling | 50 | 50 | 0 | 11 | 66 | 23 |
| Metabolomics | 53 | 47 | 0 | 11 | 78 | 11 |
| Proteomics | 64 | 36 | 0 | 29 | 60 | 11 |
| Systematic Family History | 17 | 36 | 46 | 6 | 23 | 71 |
| Genetic Counselors | 23 | 47 | 30 | 6 | 17 | 77 |
| Electronic Medical Record | 23 | 47 | 30 | 6 | 0 | 94 |
| Clinical Decision Support | 33 | 33 | 33 | 6 | 0 | 94 |

Table 2. Barriers to genomic medicine implementation.

- Lack of evidence of efficacy or effectiveness of genomic interventions and related co-dependent technologies*
- High cost and/or lack of reimbursement for tests and co-dependent technologies
- Need for evidentiary thresholds for genomic testing
- Lack of consensus on what investments are needed in research and health care capacity for effective, sustainable implementation
- Limited access to educational information
- Lack of bioinformatics/EMR infrastructure to order, receive, act upon, and follow up results and assess impact of clinical interventions
- Lack of expertise and training programs in genetics, genomics, informatics, and/or statistics
- Need for quality control standards for genome technologies
- Need for databases with genomic variants linked to clinical phenotypes
- Limited access to reliable standardized genotyping or sequencing platforms
- Concern over consent and privacy needs
- Need to align genomic research with the future burden of disease and health needs of patients and populations
- Need to align development of genomic tests with development of effective co-dependent technologies
- Need to consider ethical and legal aspects of the 'ownership' of genomic information
- Need to manage competing interests in a fair and transparent manner

* Co-dependent technologies: Health technologies that depend on another technology to achieve or enhance their intended effect, such as a diagnostic test used to determine the patient subgroup most likely to respond to a new medication [82].

Table 3. Examples of specialized genomic medicine implementation projects in participating countries and regions.

| Country (Name of Project) | Goals of Specialized Programs |
|---|--|
| <u>Single Country Efforts</u> | |
| Australia | Develop national framework for translating –omics discoveries into clinical research and practice, including advice on return of results from genomics research and clinical testing |
| Belgium (Belgian Medical Genomics Initiative, BeMGI) | Create national framework for clinical exome sequencing, share variant frequency data, incorporate into international initiatives, train the next generation of researchers and clinicians [http://www.bemgi.be/] |
| Canada (Genomics and Personalized Health Competition) | Assess benefits (including economic benefits) of genomic technology to patients and expand capacity for clinical and translational research in 17 diverse projects [http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx] |
| Estonia (Estonian Program for Personal Medicine) | Sequence 5K individuals, develop Estonian genotyping array, pilot of 50K Estonian Biobank members, offer to all 35-65 yo (~500K) and link to EMR |
| France | Create national network of molecular genetics laboratories, clinical cancer genetics centers, and inter-regional sequencing platforms |
| India | Develop infrastructure for genomic medicine implementation including disease susceptibility assessment across ethnic groups, fetal risk prediction and anomaly diagnosis, and cancer genomics |
| Israel | Use genomics in cancer treatment, push de-identified family history data into EMR of relatives |
| Japan (Implementation of Genomic Medicine Project, IGMP) | Use genomics for optimized diagnosis, treatment and prevention |
| Korea (Genome Technology to Business Translation Program) | Use genomics to develop early diagnosis and treatment approaches for personalized and preventive medicine |

| | |
|---|---|
| Luxembourg (Centre for Systems Biomedicine) | National Centre of Excellence in Early Diagnosis and Stratification of Parkinson's Disease |
| Singapore (POLARIS) | Pilot <i>TGFBI</i> testing for disease diagnosis and family risk assessment in stromal corneal dystrophies, then implement 90-gene panel for gastrointestinal cancers |
| Sri Lanka | Use SNP genotyping to identify thalassemia carriers and genetic modifiers to convert thalassemia to manageable, chronic illness |
| Thailand (Pharmacogenomics and Personalized Medicine) | Implement PGx card to identify risk for top ten drugs with risk for Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), integrated with nationwide pharmacovigilance program |
| United Kingdom (Genomics England) | Sequence 100K whole genomes and link to National Health Service records to treat individual patients and better understand cancer, rare and infectious diseases [http://www.genomicsengland.co.uk/] |
| <hr/> <u>Multi-National Efforts</u> | |
| Genomic Medicine Alliance | Build collaborative efforts between developed and developing/low-income countries, genotype pharmacogenomically relevant variants in developing nations, develop national/ethnic genetic databases using a data warehouse approach, engage in public health genomics projects |
| Gulf States (Genatak) | Laboratory network for pre-marital, pre-natal and post-natal detection of recessive diseases, genetic counseling, personalized cancer treatment, chronic disease risk |

Table 4. Opportunities for international collaborations.

Evidence generation

- Catalog ongoing evidence-generating projects
- Assess availability of data and specimens
- Define standards for evidence
- Establish standards for genetic and genomic tests
- Encourage development of professional practice guidelines
- Identify countries/systems willing to enable access to patient data
- Develop systems to capture outcomes from EMRs and other clinical systems

Health information technology

- Define key elements that should be stored in EHR
- Identify and share existing IT solutions that are more robust and generalizable (clinical decision support, variant databases, informatics pipelines)
- Develop global resource for actionable clinical variants
- Define and link necessary federated databases needed to implement genomic medicine
- Collect and aggregate gene and variant data (e.g. EVS, ClinVar)
- Develop controlled vocabulary for phenotypes (ontology); identify available ontologies
- Establish clearinghouse of genomic medicine implementation guidelines

Education/workforce development

- Genomics professionals
 - Collect data on genomic professional workforce and training in different countries
 - Summarize existing workforce surveys and conduct new ones as needed
 - Share competencies and training paradigms
 - Compare training paradigms for geneticists and identify best practices
 - Examine extending current capabilities by telemedicine and other remote approaches
- Other health professionals
 - Examine curricula and determine where genetics competency training can be accommodated
 - Define necessary genomic competencies for trainees at completion of training, which may differ across regions/countries
 - Deploy new educational tools, such as distance learning
 - Develop region/country-specific teaching materials, perhaps on common templates
- Public
 - Adapt existing products and activities such as DNA Day to specific cultures
 - Extend to students at secondary school level
 - Engage patient support groups to sponsor programs, develop and distribute educational materials

- Provide clearinghouse for accumulated educational resources
- Consider novel educational paradigms

Pharmacogenomics

- Promote improved quality of evidence base for pharmacogenomics implementation
- Prioritize for study and implementation inexpensive drugs with risk of treatment failure or severe adverse drug reactions likely to be limited to genetically defined subset
- Develop and pilot large-scale implementation project around successful programs such as global eradication of genetically-mediated SJS/TEN

Policy

- Data sharing and regulatory issues
 - Map current activities and issues being addressed
 - Perform gap analysis
 - Establish “network of networks” in policy development to share information
- Costs and benefits
 - Identify burdens of disease and points in care pathway where genomic tools would integrate and have the greatest impact on outcomes
 - Improve capacity for conducting convincing economic, feasibility, and sustainability analyses
 - Perform economic, feasibility, and sustainability analyses from perspective of different stakeholders such as payers, delivery systems, national health services
 - Engage payers and payment decision processes
 - Work in and learn from systems with one or a few centralized payers